Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-3 and 5-13 are pending in the application, with claim 1 being the independent claim. Claim 4 is sought to be cancelled without prejudice to or disclaimer of the subject matter therein. New claims 12 and 13 are sought to be added. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Support for Amended and New Claims

Support for amended claims 1 and 5 can be found, *inter alia*, in the specification at page 13, lines 19-24, at page 14, lines 3-5, at page 15, lines 11-23, at page 19, line 22, through page 20, line 10, and in original claims 1 and 5, respectively. Support for amended claims 2 and 3 can be found, *inter alia*, in the specification at page 13, line 19-24, and in original claims 2 and 3, respectively. Support for amended claim 11 can be found, *inter alia*, in the specification at page 19, line 22, through page 20, line 21, and in original claim 11. Support for new claims 12 and 13 can be found, *inter alia*, in the specification at page 19, line 22, through page 20, line 21, and in original claim 11.

II. Rejections under 35 U.S.C. § 112, First Paragraph: Written Description

The Examiner rejected claims 1-3 and 7-11 under 35 USC § 112, first paragraph, because, according to the Examiner, these claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. *See* Paper No. 6, page 2. According to the Examiner,

> *Apart from the disclosure of utilizing antifolate drugs* that are capable of being polyglutamated by the FPGS gene product to enhance their cytotoxicity or increasing their therapeutic efficacy such as methotrexate, [and] edatrexate, the instant specification fails to teach any other chemotherapeutic agents (small organic compounds, peptides, polypeptides, nucleic acids or carbohydrates) that are capable of being activated by the FPGS gene product to effect the killing of neoplastic cells.

Id. at page 3 (emphasis added). Applicants respectfully traverse the rejection.

Solely to expedite prosecution and without acquiescing to the appropriateness of this "written description" rejection, Applicants have amended claim 1 such that the term "chemotherapeutic agent" is replaced with "antifolate drug." Accordingly, the rejection under 35 USC § 112, first paragraph, for insufficient written description is rendered moot and should be withdrawn.

III. Rejections under 35 U.S.C. § 112, First Paragraph: Enablement

The Examiner rejected claims 1-11 under 35 USC § 112, first paragraph, because, according to the Examiner, the specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. *See* Paper No. 6, page 5.

The Examiner provides four separate grounds for rejecting Applicants' claims under 35 USC § 112, first paragraph, based on lack of enablement. Applicants address each of these grounds in turn below.

A. Chemotherapeutic Agents

The Examiner stated that

> [t]he broad claims encompass any and all chemotherapeutic agent that is activated by the FPGS gene to enhance its cytotoxic or therapeutic effects with respect to killing neoplastic cells. The present specification is not enabled for the full scope of the method as claimed for the reason set forth in the Written Description section above. Given the lack of guidance provided by the instant specification regarding to [sic] any other chemotherapeutic agent other than the antifolate drugs that are substrates of the FPGS gene product, it would have required undue experimentation for one skilled in the art to make and use the method as claimed.

Paper No. 6, page 6, last paragraph.

Applicants note that claim 1 has been amended such that the term "chemotherapeutic agent" is replaced with "antifolate drug." Thus, this ground for rejection under 35 USC § 112, first paragraph, is rendered moot and should be withdrawn.

B. In Vivo Delivery of a Genetic Vector

The Examiner asserted that the full scope of the claims is not enabled because the claims "encompass any and all routes of delivering a vector comprising an FPGS gene into neoplastic cells *in vivo*," and that "vector targeting *in vivo* to desired cells or tissues. . . for

achieving therapeutic effects continues to be unpredictable and inefficient." *See* Paper No. 6, page 7. In support of this position, the Examiner cited four references that are intended to illustrate the technical difficulties associated with delivering genetic vectors to target cells *in vivo* by methods other than direct intratumoral injection (Dang, C.V., *et al.*, *Clin. Cancer Res.* *5*:471-474 (1999); Miller, N. and Vile, R., *FASEB J.* *9*:190-199 (1995); Deonarian, M.P., *Exp. Opin. Ther. Patents* *8*:53-69 (1998); and Verma, I.M. and Somia, N, *Nature* *389*:239-242 (1997)).

Applicants assert that the references cited by the Examiner merely set forth technical hurdles that need to be overcome in order to *increase the efficiency* with which genetic vectors are targeted to cells *in vivo*. They do not, however, indicate that genetic vector delivery to target cells is impossible or infeasible. Deonarian, in fact, describes experimental results in which genetic vectors were successfully delivered to liver cells *in vivo* using ligand-targeted receptor-mediated endocytosis of polyplexes:

> Reporter gene delivery experiments *in vivo* showed 85% of the injected DNA was taken up by the liver by 10 min. A great deal of research has followed, including *in vivo* gene delivery of albumin to rats with LDL receptor deficiency. An average of 1000 copies of the plasmid were found per hepatocyte resulting in a level of 34 μg/ml human albumin in the serum of animals 2 - 4 weeks after injection and partial hepatectomy.

Deonarian at 59, left column. In addition, the Dang reference concludes with the following sentence: "Whereas setbacks in gene therapy were clearly recognized and discussed, there was a unique level of enthusiasm that many of these obstacles could be overcome with meticulously designed basic and clinical studies." *See* Dang at page 474, right column.

Therefore, the references cited by the Examiner actually support, rather than refute, Applicants' contention that the specification enables the full scope of the claims.

The Examiner has grounded the enablement rejection on the alleged low efficiency with which genetic vectors can be delivered *in vivo*; the Examiner does not contend that *in vivo* gene delivery is generally impractical. For example the Examiner stated that

> [t]he instant specification fails to teach one of skilled [sic] in the art how to overcome the unpredictability for *in vivo* vector targeting, such that an *efficient transfer and expression* of a FPGS gene could be achieved in neoplastic cells of solid or non-solid tumors through any and all routes of delivery such that upon treatment with a chemotherapeutic agent, the agent is activated by the FPGS gene product to effect the killing of said neoplastic cells.

Paper No. 6, page 8 (emphasis added).

Applicants note that to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, a specification need only enable the "*full scope* of the claimed invention." *In re Wright*, 999 F. 2d 1557,1561 (Fed. Cir. 1993) (emphasis added). Furthermore, "as concerns the breadth of a claim relevant to enablement, the only concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims." MPEP § 2164.08.

There is nothing in Applicants' claims requiring that the vector for gene delivery be delivered into neoplastic cells with any particular minimum level of efficiency. In fact, as was recognized in the art at the time of Applicants' application, a major advantage associated with gene delivery systems utilizing so called "suicide genes," such as FPGS, is that only a low level of gene delivery is required to exert anti-neoplastic effects.

> Suicide genes are used in a significant number of the cancer trials because they have a number of advantages. (1) Suicide

> genes and their prodrug are toxic to chemotherapy resistant tumors. (2) Only short-term gene expression is required. *(3) Only a fraction of the tumor cells within the tumor mass (>10%) needs to express the suicide gene to kill the entire tumor.* (4) Gene-modified tumor cells that die after exposure to the prodrug stimulate an immune response, which in some cases has been shown to be stronger than that to irradiated tumor cells. Taken together, these characteristics allow for cytoreduction of the tumor mass through "molecular surgery" by killing the tumor cells that have been genetically modified with the suicide gene.

Freeman, S.M., *et al.*, *Semin. Oncology 23*:31-45 (1996) (emphasis added, Table references omitted; cited and incorporated by reference in the specification at page 4, line 10, and listed in the Information Disclosure Statement filed on November 2, 2000); *See also* Verma and Somia at 239 ("In the brain, however, gene transfer to *just a few hundred cells* could considerably benefit patients with neurological disease," emphasis added). Thus, as recognized by those skilled in the art, the successful application of the invention does not require high levels of efficiency of genetic vector delivery.

Moreover, there are several examples in the literature at the time the present application was filed that demonstrate the effectiveness of *in vivo* genetic vector delivery by methods other than direct inoculation of tumors. For instance, Deonarian, discussed above, describes successful results involving the *in vivo* delivery of genetic vectors to liver cells. As another example, Lan *et al.*, *Cancer Res. 57*:4279-4284 (1997), demonstrated the delivery of an i.p.-administered adenoviral vector to gastric carcinoma cells. (Lan was cited and incorporated by reference in the specification at page 21, line 19, and was listed in the Information Disclosure Statement filed on November 2, 2000). In addition, Nakanishi, *Crit. Rev. Therapeu. Drug Carrier Systems 12*:263-310 (1995), provides an overview of systems for gene transfer into tissue cells and summarizes several studies which illustrate the *in vivo*

delivery of retroviral, adenoviral, adeno-associated viral, and herpesviral vectors. Nakanishi further summarizes the state of *in vivo* gene transfer as of 1995:

> *In vivo* gene transfer is an approach to transfect tissue cells *in situ* by introducing gene transfer vectors through direct injection, through perfusion with catheters, or through an intravenous injection. This approach is more practical than *ex vivo* gene transfer and will become the major route for therapeutic gene transfer in the future. *In vivo* transfer may be applied to a wide variety of tissues and cells, and many vector systems other than retroviral vectors have been reported to be adopted for *in vivo* transfection.

Nakanishi at page 267 (Nakanishi was cited and incorporated by reference in the specification at page 16, lines 10-11, and was listed in the Information Disclosure Statement filed on November 2, 2000). Thus, the state of the art as of the effective filing date of the present application clearly indicates that the *in vivo* delivery of genetic vectors to target cells by methods besides direct inoculation is feasible and has important clinical applications in the field of gene therapy.

To summarize, the references cited by the Examiner in support of the rejection merely indicate that, in certain contexts, technical difficulties may exist that impede the delivery of genetic vectors with optimum efficiency. Applicants' claims, however, do not specify any minimum level of genetic vector transfer efficiency. The Examiner has not established that the *in vivo* delivery of genetic vectors by methods other than direct injection is of such low efficiency so as to be regarded as impracticable. In fact, at the time the present application was filed, the scientific literature (including even the references cited by the Examiner) was replete with examples of successful *in vivo* genetic vector delivery using methods other than direct injection; that is, it would not require undue experimentation for a skilled artisan to practice the full scope of Applicants' invention, including the delivery of

genetic vectors by *in vivo* methods. The Examiner has not met his burden in establishing a *prima facie* case of non-enablement. Therefore, in addition to *in vitro* genetic vector delivery and the delivery of genetic vectors by direct inoculation, Applicants' claims are fully enabled with respect to *in vivo* genetic vector delivery methods.

C. Replication Competent Viral Vectors

The Examiner also asserted that the present claims "encompass the use of replication competent viral vectors," but that "[n]either the instant specification nor the prior art at the effective filing date of the present application teaches the use of replication competent viral vectors such as retrovirus, adenovirus or lentivirus (HIV-1 and HIV-2) for achieving therapeutic results via gene therapy." *See* Paper No. 6, page 9. The Examiner further suggests that the use of replication competent viral vectors would impede the practice of the claimed methods:

> It is unclear whether the treated individual having neoplastic cells succumbs to the cytotoxic effects of replication competent viral vectors prior to any therapeutic effects contemplated by Applicants could be attained by the methods as claimed. Furthermore, neoplastic cells infected with replication competent viruses could be lysed prior to any effective accumulation of polyglutamated antifolates could be attained to effect the killing of neoplastic cells as contemplated by the present invention.

Paper No. 6, page 9.

In essence, the Examiner has based the enablement rejection on the presence of alleged inoperative embodiments, *i.e.*, methods for killing neoplastic cells using replication competent viral vectors. As an initial matter, Applicants submit that the Examiner has not provided any objective evidence in support of his apparent conclusion that the use of

replication competent viral vectors would interfere with the practice of the claimed methods. Therefore, the Examiner has not satisfied his burden in establishing a *prima facie* case of non-enablement. *See In re Wright,* 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Moreover, Applicants note that the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled.[1] *See Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984). The standard is whether a skilled artisan could determine which embodiments of the claimed invention would be inoperative or operative with expenditure of no more effort than is normally required in the art. *See id.*, *see also In re Angstadt*, 537 F.2d 498, 502-503, 190 USPQ 214, 218 (CCPA 1976).

Here, Applicants assert that it would take no more than minimal effort on the part of the skilled artisan to ascertain which viral vectors would and would not be appropriate for use within the scope of the claimed invention. The state of the art as of the effective filing date of the present application was such that the various classes and variants of viral vectors (and other vehicles for the delivery of genetic material to cells) were well defined and understood. *See, e.g.,* Nakanishi, *supra*, for an overview of various methods for gene transfer into cells. Accordingly, it is unnecessary for Applicants to expressly exclude from the scope of the present claims the use of certain classes of viral vectors (*e.g.*, replication competent

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[1]As noted by one commentator, "nearly all claims can be read on inoperative embodiments if one is deliberately setting out to sabotage the invention." Janicke, "Patent Disclosure -- Some Problems and Current Developments (Part II)," 52 J. Pat. Off. Soc'y 757, 772-773 (1970).

viral vectors) that, in some contexts, may detract from or interfere with the practice of the claimed methods.

D. Mammalian Artificial Chromosomes

The Examiner asserted that "[t]he instant claims encompass the use of mammalian artificial chromosomes as a non-viral gene delivery of FPGS gene for killing neoplastic cells," but that "the instant specification fails to provide any specific teachings regarding to [sic] the making or using of any mammalian artificial chromosome for killing a neoplastic cell in a method as claimed." *See* Paper No. 6, pages 9-10.

Applicants note that they are not limited to the confines of the specification to provide the necessary information to enable the invention. *See In re Howarth*, 654 F.2d 103, 105-6, 210 USPQ 689, 692 (CCPA 1981). Furthermore, an Applicant need not supply information that is well known in the art. *Id.*, 654 F.2d at 105-6, 210 USPQ at 692; *see also In re Brebner*, 455 F.2d 1402, 173 USPQ 169 (CCPA 1972) (finding a disclosure enabling because the procedure for making the starting material, although not disclosed, would have been known to one of ordinary skill in the art as evidenced by a Canadian patent). "'That which is common and well known is as if it were written out in the patent and delineated in the drawings.'" *Howarth*, 654 F.2d at 106, 210 USPQ at 692 (quoting *Webster Loom Co. v. Higgins et al.*, 105 U.S. (15 Otto.) 580, 586 (1881)). In addition, one of ordinary skill in the art is deemed to know not only what is considered well known in the art, but also where to search for any needed starting materials. *Id.*

Applicants assert that the construction and use of mammalian artificial chromosomes was well known in the art as of the effective filing date of the present application. *See e.g.*,

Specification at page 20, line 9-10 (citing Ascenzioni, *et al., Cancer Lett. 118*:135-142 (1997), which provides an overview of the technology regarding mammalian artificial chromosomes). Thus, it would have been unnecessary, indeed improper, for Applicants to provide detailed instructions regarding the construction of mammalian artificial chromosomes.

The Examiner cites a passage from Calos, *Trends Genet. 12*:463-466 (1996), that supposedly lends support to the conclusion that "it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention." *See* Paper No. 6, page 10. The passage cited from the Examiner is as follows:

> A vector of this size is far beyond the size of vectors in current use for gene therapy and poses problems of major dimensions, particularly for the manufacture and delivery of vector DNA. Therefore, while construction of artificial chromosome vectors has not yet been realized, once it is, a series of challenging technical barriers will have to be surmounted before such molecules could reasonably be used as gene therapy vectors.

Calos at page 464, right column.

Applicants note that, in the above-quoted passage, the author is referring to artificial chromosomes created by a very specific strategy, namely, the progressive reduction of existing chromosomes using telomere-mediated fragmentation. *See id.* Moreover, when read in its full context, the author's statement amounts to, at most, an educated guess as to the minimum size that might be achieved for an artificial chromosome based on the *prediction* that "[t]he final size [of an artificial chromosome produced by telomere-mediated fragmentation] will *probably* be driven primarily by the minimal size of a stable centromere, *which appears* to be about 1 Mb." *See id,* (emphasis added).

Therefore, the only conclusion that can be reasonably drawn from the statements in Calos is that technical difficulties *may* be encountered in the production of artificial chromosomes when they are generated by the progressive reduction of existing chromosomes using telomere-mediated fragmentation, *assuming* that the minimal size of a stable centromere, is about 1 Mb. Applicants maintain that such tentative conclusions do not suggest that the practice of the claimed invention insofar as it encompasses the use of mammalian artificial chromosomes would require any more than routine experimentation.

Even if the Examiner's assessment of mammalian artificial chromosomes was correct, however, (a proposition which Applicants explicitly traverse), the rejection would amount to no more than an rejection on the basis of an alleged inoperative embodiment[2]. As stated above, the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled. *See Atlas Powder Co.*, 750 F.2d at 1577, 224 USPQ at 414. A rejection for lack of enablement on the basis of an inoperative embodiment is only proper when it is shown that a skilled artisan would require more than routine experimentation to distinguish the inoperative from the operative embodiments. *See id.*

With respect to the present claims, the Examiner has provided no evidence or arguments to suggest that the reasonable practice of the claimed invention would be substantially impeded due to the presence of mammalian artificial chromosomes within the scope of the claims. Nor has the Examiner set forth any indication that it would require

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[2]Applicants note that the only claim that explicitly defines the vector for gene delivery as a mammalian artificial chromosome is claim 11 wherein a mammalian artificial chromosome is included within a Markush group of vectors for gene delivery. In the remainder of the claims, the use of mammalian artificial chromosomes is merely an alleged inoperative embodiment.

undue experimentation to distinguish the operative from the supposed inoperative embodiments of the claimed invention. Accordingly, the presence of mammalian artificial chromosomes within the scope of the present claims does not provide a permissible basis of rejection under 35 USC § 112, first paragraph.

E. Summary

Applicants assert that the Examiner, in providing the four grounds of rejection discussed above, has not met his initial burden of establishing a reasonable basis to question the enablement provided for the claimed invention. *See In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Accordingly, Applicants respectfully request that the rejection under 35 USC § 112, first paragraph, for lack of enablement, be reconsidered and withdrawn.

IV. Rejections under 35 USC § 112, Second Paragraph

The Examiner rejected claims 1-11 under 35 USC § 112, second paragraph, because, according to the Examiner, these claims are indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. *See* Paper No. 6, page 10. Applicants respectfully traverse the rejection.

A. The Rejection of Claim 1

The Examiner asserted that in claim 1, and in claims dependent thereon, the phrase "said neoplastic cells" in steps (b) and (c) is unclear. *See* Paper No. 6, page 10. The

Examiner also stated, "as recited in step (a), there is no requirement that neoplastic cells infected with a vector comprising an FPGS gene express the FPGS gene product." *See id.*, page 11. Finally, the Examiner stated that "it is unclear what is encompassed by the phrase 'an FPGS gene'. This is because it is not clear what is the beginning or end of an FPGS gene." *See id.* Applicants respectfully traverse these assertions.

Nevertheless, solely to expedite prosecution, Applicants have amended claim 1. In its amended version, steps (b) and (c) make explicit that the neoplastic cells referred to are "said neoplastic cells containing said nucleotide molecule." Applicants have also substituted the term "FPGS gene" in claim 1(a) with the phrase "a nucleotide molecule that encodes folylpolyglutamyl synthetase (FPGS)." In addition, Applicants have included in step (a) the phrase "wherein said nucleotide molecule directs the production of said FPGS in said neoplastic cells containing said nucleotide molecule." These amendments are intended to make explicit the fact that the neoplastic cells containing the vector express the FPGS gene product. Thus, all of the Examiner's rejections of claim 1 under 35 USC § 112, second paragraph, have been accommodated by the amendment to this claim and should, accordingly, be withdrawn.

B. The Rejection of Claim 11

The Examiner asserted that, in claim 11, the phrases "the direct injection of nucleic acid," "particle-mediated gene transfer," and "receptor-mediated gene transfer" render the claim indefinite. *See* Paper No. 6, page 11. According to the Examiner, these phrases "indicate routes or methods of gene delivery and not to a non-viral vector as recited in claim 10 from which claim 11 is dependent upon." *See id.* In addition, the Examiner stated that

"[i]t is also unclear why 'DNA-adenovirus conjugate' is considered to be a non-viral vector because clearly it contains a virus component, adenovirus." *See id.* Finally, the Examiner asserts that "it is unclear what is encompassed by the phrases 'endothelial cell' and 'macrophage'." *See id.* Applicants respectfully traverse these assertions.

Applicants first note that the phrases "the direct injection of nucleic acid," "particle-mediated gene transfer," and "receptor-mediated gene transfer" have been removed from claim 11. These expressions have now been incorporated into new claim 13 which is directed to the method of claim 1, wherein the vector for gene delivery is delivered into said neoplastic cells by the methods encompassed by these three expressions. The Examiner's rejection based on the inclusion of these expressions in claim 11 is accordingly rendered moot.

Applicants also note that claim 11 has been amended in that it no longer depends from claim 10; claim 11, as amended, now depends from claim 1. Consistent with this change in dependency, the term "non-viral" has been deleted from claim 11. Thus, the Examiner's statement regarding "DNA-adenovirus conjugate" is moot.

Finally, in regard to the Examiner's comments regarding the terms "endothelial cell" and "macrophage" in claim 11, it appears that the Examiner has confused the use of these vehicles *as vectors per se* with their potential use in conjunction with *ex vivo* gene therapy applications. Applicants direct the Examiner's attention to the specification at page 20, lines 14-20, and the references incorporated by reference therein (Rancourt *et al., Clin. Cancer Res. 4*:265-270 (1998); Ojeifo *et al., Cytokines Mol. Ther. 2*:89-101 (1996); Zufferey *et al., Nat. Biotechnol. 15*:871-875 (1997); and Naldini *et al., Science 272*:263-267 (1996)). These references describe the use of endothelial cells and macrophages as vectors for *in vivo* (as

distinguished from *ex vivo*) gene delivery. Thus, in view of the teachings of these references (which were available to those skilled in the art as of the effective filing date of the present application), Applicants submit that the inclusion of endothelial cells and macrophages as vectors for gene delivery does not render claim 11 indefinite.

In view of the foregoing, Applicants respectfully request that the rejection of claim 11 under 35 USC § 112, second paragraph, be reconsidered and withdrawn.

V. Rejections under 35 U.S.C. § 103

The Examiner rejected claims 1-11 under 35 USC § 103(a), because, according to the Examiner, these claims are unpatentable over Kim, *et al.*, *J. Biol. Chem. 268*:21680-21685 (1993) ("Kim") as evidenced by Osborne, *et al.*, *J. Biol. Chem. 268*:21657-21664 (1993) ("Osborne"), in view of Garrow, *et al.*, *Proc. Nat'l. Acad. Sci. 89*:9151-9155 (1992) ("Garrow"); and Roth and Christiano, *J. Nat'l. Cancer Inst. 89*:21-39 (1997) ("Roth"). *See* Paper No. 6, page 12. Applicants respectfully traverse the rejection.

Kim (as evidenced by Osborne) teach that mutant CHO cells lacking FPGS activity exhibit increased sensitivity to pulses of MTX in cell culture after being transfected with an FPGS expression cassette. As acknowledged by the Examiner, Kim does not teach the delivery of a vector comprising a nucleotide molecule that encodes an FPGS into *neoplastic cells.*

Garrow describes the cloning of a human FPGS. Garrow teaches that transfecting the cloned FPGS into mutant CHO cells lacking FPGS activity restored the ability of the transfected mutant cells to grow in culture in the absence of purines and thymidine. Garrow

does not teach the delivery of a vector comprising a nucleotide molecule that encodes an FPGS into *neoplastic cells*. Nor does Garrow teach the treatment of cells expressing FPGS with an antifolate drug.

Roth provides a general overview of approaches to gene therapy for cancer. Roth does not teach the delivery into neoplastic cells of a vector comprising a nucleotide molecule that encodes an FPGS. Nor does Roth teach the application of antifolate drugs in the context of anti-cancer gene therapy.

Rejection of claimed subject matter as obvious under 35 U.S.C. § 103 in view of a combination of references requires (1) consideration of whether prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or carry out the claimed process, and (2) whether the prior art would also have revealed that such a person would have reasonable expectation of success; both suggestion and reasonable expectation of success must be found in the prior art, not in Applicant's disclosure. *See In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Further, all claim limitations must be taught or suggested by the prior art. *In re Royka*, 180 USPQ 580 (CCPA 1974).

Applicants assert that, with respect to the present claims, the Examiner has not established a *prima facie* case of obviousness because he has not pointed to anything, in the cited references or in the body of knowledge generally possessed by those skilled in the art, that would suggest the modification or combination of the references to arrive at Applicants' claimed invention.

The Examiner provided the following justification for the rejection:

> One of ordinary skill in the art would have been motivated to carry out the above modification [*i.e.*, transfecting or transforming a vector comprising a DNA sequence encoding

> FPGS into neoplastic cells] with a reasonable expectation of success because on the basis of their findings, Kim *et al.* noted that the ability of cells to metabolize MT to longer chain length derivatives enhances cytotoxicity when MTX is infused for a limited period and then removed, which mimics clinical usage, and that larger effects of FPGS activity levels on the cytotoxicity of antifolates that require polyglutamylation for effective inhibition of target enzymes were also obtained (page 21683, col. 2, last paragraph). Furthermore, as taught by Kim *et al.*, lowered FPGS activity and decreased polyglutamylation of antifolates may be general mechanisms by which cancer cells become resistant to a wide range of antifolates. The production and cloning of replication defective viral vectors and non-viral vectors comprising a cDNA sequence encoding FPGS are methods common to molecular biology and the *in vivo* aspect of the present invention would have been within the scope of skills of an ordinary artisan at the time of the instant invention as evidenced by the teachings of Roth & Christiano.

Paper No. 6, pages 14-15 (emphasis in original).

The Examiner's justification for the rejection under § 103 is essentially no more than a restatement of the teachings of Kim which, by the Examiner's own admission, is deficient in that it does not teach the delivery of an FPGS gene to neoplastic cells. The Examiner in explaining the rejection has pointed specifically to the statement in Kim indicating that "[l]owered FPGS activity may be a general mechanism by which cells can become resistant to a wide range of antifolates," and that "[r]esistance to MTX by this mechanism has recently been reported for a human leukemia cell." *id* at 21684. There is no suggestion, however, that such MTX resistance could be counteracted by delivering an FPGS gene to neoplastic cells. Thus, these statements do not provide the requisite motivation to modify or combine the references as required to support a rejection under 35 USC § 103(a).

In addition, Applicants assert that there would have been no reasonable expectation of success in addressing the problem of MTX resistance by delivering an FPGS gene to

neoplastic cells since lowered FPGS activity was only a hypothetical cause of the resistance. From the perspective of the skilled artisan, other equally likely explanations could have existed for the MTX resistance observed in certain cells.

Applicants contend that the Examiner has not provided a sufficient explanation as to why a person skilled in the art would have been motivated to modify the teachings of Kim or Garrow such that the cloned FPGS gene is delivered, not to a mutant Chinese hamster ovary cell, but to a *neoplastic cell*. In addition, the Examiner has not provided any explanation as to why a skilled artisan would have been motivated to modify the general teachings of Roth such that a nucleotide molecule that encodes an FPGS is delivered to a neoplastic cell followed by treatment of the neoplastic cell with an antifolate drug.

Since there is no motivation to modify or combine the cited references to arrive at Applicants' claimed invention, and the Examiner has failed to point to any such motivation, a *prima facie* case of obviousness has not been established. Accordingly, Applicants respectfully request that the rejection of claims 1-11 under 35 USC § 103(a) be reconsidered and withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

1. (Once amended) A method for killing neoplastic cells, said method comprising:

(a) [infecting] delivering into said neoplastic cells [with] a vector for gene delivery, said vector comprising [an FPGS gene] a nucleotide molecule encoding folylpolyglutamyl synthetase (FPGS), wherein said nucleotide molecule directs the production of said FPGS in said neoplastic cells containing said nucleotide molecule;

(b) treating said neoplastic cells containing said nucleotide molecule with an antifolate drug [a chemotherapeutic agent that is activated by the product of said FPGS gene]; and

(c) killing said neoplastic cells containing said nucleotide molecule.

2. (Once amended) The method of claim 1, wherein said FPGS [gene] is a mammalian [gene] FPGS.

3. (Once amended) The method of claim 2, wherein said mammalian [gene] FPGS is a human [gene] FPGS.

5. (Once amended) The method of claim [4] 1, wherein said antifolate drug is methotrexate, edatrexate, aminopterin, or a thymidylate synthetase inhibitor.

11. (Once amended) The method of claim [10] 1, wherein said [non-viral] vector for gene delivery is a prokaryotic vector, a cationic liposome, a fusogenic liposome, a DNA-adenovirus conjugate, a DNA-protein complex, a non-viral T7 autogene vector, [the direct injection of nucleic acid, particle-mediated gene transfer, receptor-mediated gene transfer,] a starburst polyamidoamine dendrimer [dendrimers], a cationic peptide, a mammalian artificial chromosome, an endothelial cell, or a macrophage.

Claim 4 has been cancelled.

Claims 12 and 13 have been added.